Advisory Committee to the Director
Working Group on NIH Oversight of Clinical Gene Transfer Research
Interim Report

Recommendations Regarding Review of Gene Transfer Protocols

June 8, 2000

Gene therapy is a set of approaches to the treatment of human disease that encompasses a variety of techniques directed toward therapeutic ends. For instance, gene therapy may be used to: 1) alter or supplement the function of a mutated gene by providing a copy of a normal gene; 2) directly alter and/or repair the mutated gene; or 3) provide a gene that adds missing functions or regulates the expression of other genes. As an extension of conventional medical therapy, the goal of gene therapy is to treat disease in an individual patient by the administration of DNA rather than a drug. The success of this technology is dependent upon not only the delivery of genetic material into the target cells, but also the expression of the gene once it reaches its target site. Both of these requirements pose considerable technical challenges. With regard to gene delivery to target cells, a variety of "vectors" have been developed to serve this purpose. Most of these vectors are disabled viruses that work by delivering genes into certain human cell types, in much the same way as ordinary viruses infect cells. Because only somatic cells, and not germ cells (eggs and sperm), are the target of these efforts, gene transfer is intended to affect only the individuals under treatment and not their offspring. While the field of gene transfer research is expanding rapidly, there is much clinical research still to be done.

Recent Events

In September 1999, Jesse Gelsinger, an 18-year-old patient enrolled in an adenoviral vector gene transfer clinical protocol, died—not as a result of his underlying condition, but as a direct result of administration of a gene transfer product. In the 10-year history of clinical gene transfer, this is presumed to be the first death directly related to the gene transfer itself. The death of this young man prompted concern about the processes by which gene transfer trials are reviewed, conducted, and monitored by the Food and Drug Administration (FDA) and the National Institutes of Health (NIH) through its Office of Biotechnology Activities (OBA) and advisory body, the Recombinant DNA Advisory Committee (RAC).

In response to this concern, then NIH Director, Dr. Harold Varmus, established the Advisory Committee to the Director Working Group on NIH Oversight of Clinical Gene Transfer Research to review the role of NIH in oversight of clinical gene transfer research, including the initial review of gene transfer protocols.

Current Oversight of Gene Transfer Research

Gene transfer clinical trials are unique in that they undergo review by both NIH and FDA. NIH's oversight process is conducted by RAC and through the *NIH Guidelines for Research Involving Recombinant DNA Molecules* (the *NIH Guidelines*). FDA regulations apply to all clinical gene transfer research; whereas, NIH/OBA governs gene transfer research that is supported with NIH funds or conducted at or sponsored by institutions that receive funding for recombinant DNA research. Currently, the majority of gene transfer research is subject to the *NIH Guidelines*.

An investigator is permitted to enroll subjects in a clinical gene transfer protocol as soon as FDA authorizes an Investigational New Drug (IND) application and approval to proceed has been granted by an Institutional Review Board (IRB) and an Institutional Biosafety Committee (IBC). The IRB is governed by the Federal Policy for the Protection of Human Subjects (45 CFR 46) and reviews human subjects research conducted with federal funds or at institutions that receive federal funds. The IBC is governed by the *NIH Guidelines* and is responsible for and authorized by the research institution to review and approve potentially biohazardous lines of research. It is charged with conducting an independent assessment of the containment levels required by the *NIH Guidelines* for the proposed research; assessing the facilities, procedures, practices, and training and expertise of personnel involved in recombinant DNA research; and ensuring compliance with all surveillance, data reporting, and adverse event reporting requirements required by the *NIH Guidelines*.

With regard to NIH oversight, investigators (not sponsors) must first obtain IRB and IBC approvals and then submit to OBA/RAC a copy of the proposed research protocol, which must comply with the policies and procedures for the conduct of human gene transfer clinical research set forth in the *NIH Guidelines*. Protocols that present novel scientific, ethical or safety issues are selected for public review. Currently approximately 10 percent of the submitted protocols are considered novel and undergo full RAC review.

It is important to note that in order to initiate a gene transfer trial, an investigator must obtain authorization from FDA and IRB and IBC approvals. Investigators governed by the *NIH Guidelines* are required to submit their proposals to OBA/RAC, but neither this submission nor the RAC discussion are necessary prior to the initiation of a trial.

Conclusions and Recommendations

The Working Group concluded that there must be assurance that subjects will not be enrolled in a gene transfer protocol *until* OBA/RAC has determined whether the protocol requires full RAC review and, in the case of a novel protocol, until after that review has occurred. If RAC expresses concerns about the safety or design of a novel protocol, there must be a systematic and established mechanism that allows RAC to communicate those concerns to the investigator *prior* to enrollment of subjects.

- ❑ ***Safety will be best protected if subjects are not enrolled in novel gene transfer trials until RAC discussion has occurred and its recommendations responded to by the investigator.***

- ❑ ***The timing of review of gene transfer protocols by RAC, the local IRB and IBC, and FDA should be altered to ensure that RAC functions as an effective advisory committee to investigators, institutional IRBs and IBCs, and FDA.***

- ❑ ***The requirement that the investigator obtain IRB approval prior to submission to OBA/RAC should be eliminated. This change would allow investigators to receive RAC input at an earlier stage of protocol development.***

- ❑ ***IBC approval should be withheld until RAC review is complete. In the case of non-novel protocols, IBC approval can be granted as soon as the IBC is notified that the protocol has been deemed non-novel. In the case of novel protocols, IBC approval must be withheld until after RAC discussion and the investigator has responded to the review, thereby, preventing the initiation of a trial prior to RAC review.***

In addition, the Working Group considered detailed aspects of the gene transfer protocol registration and review process and recommends the following process for the review of all gene transfer protocols.

- ❑ ***Recommended Process for RAC Review of Protocols***

1. ***Concurrent registration by the investigator of the original protocol with OBA and submission of the protocol for review to the relevant IRB and IBC. The IBC cannot grant final approval of a protocol until the RAC process has been completed.***

2. ***In addition to the protocol, the submission to OBA should include documentation of the status of IRB and IBC submission and review, and the status of the IND authorization if an application to FDA has been made. RAC should work with OPRR to encourage IRBs to consider their reviews provisional pending RAC review.***

3. ***Upon receipt of a protocol, OBA staff determines whether the application is complete and, if so, initiates the process to determine whether the protocol is novel. NIH should ask investigators to encourage sponsors to withhold application for an IND until either: 1) the proposal is deemed non-novel, or 2) the protocol has undergone the RAC review process.***

4. ***Protocols deemed non-novel are subject to the standard scrutiny and review now required by FDA for IND authorization. If RAC deems a protocol non-novel, notification is sent to the IRB, IBC, FDA, and the investigator, informing them of this determination. The IBC can now grant approval. Once an IND is authorized, the investigator should register the final protocol with OBA.***

5. *Protocols deemed novel are scheduled for public RAC review and discussion, the results of which are reported to the investigator, relevant IRB and IBC, and FDA. Following receipt of these comments, and investigator response to the RAC, the IBC can now make a decision regarding approval. IRBs should work with investigators to ensure that the results of RAC review are incorporated into the informed consent process.*

6. *The investigator is responsible for communicating with the IRB, IBC, and the sponsor and FDA, as appropriate, to prepare a publicly available response to RAC. It is assumed that the investigator will notify the sponsor, and that any FDA requirements will be followed. The investigator may submit an interim response outlining a plan that may include, for example, more pre-clinical work that may alter the protocol design enough to require a new submission at a later date. If the response is final, it must include the final IRB and IBC approval, the final consent document, the final IND (once received), and a letter describing any actions taken in response to the RAC review.*

7. *If no actions are to be taken, the response must contain a detailed explanation in support of the investigator's rationale for electing not to comply with RAC's recommendations. The investigator should copy the IRB, IBC, and FDA on the final response.*

8. *As with all gene therapy protocols, as stated in Appendix M-VII-A of the NIH Guidelines: "Upon receipt of notification of permission [from FDA] to proceed with an Investigational New Drug Application for a human gene transfer protocol, the Principal Investigator(s) shall submit a written report [to NIH OBA] that includes the following information: (1) how the investigator(s) responded to RAC's recommendations on the protocol (if applicable), and (2) any modifications to the protocols as required by the FDA." Once the IND is authorized, the protocol should be registered with OBA.*

9. *Subject enrollment begins and the protocol is entered into the NIH Human Gene Transfer database.*

Conclusions

The system envisioned above calls for open and effective lines of communication between OBA/RAC, IRBs, IBCs, research institutions, sponsors and FDA. The Working Group believes that this modified process of review serves many purposes. First, it ensures that no human subject will be enrolled in a gene transfer trial until protocol submission to OBA/RAC and, in the case of a novel protocol, until after public discussion. Second, by allowing early submission to NIH, trials need not be delayed by RAC review. Third, it allows local IRBs and IBCs to benefit from RAC review. Fourth, it retains the important function of RAC to publicly discuss novel

protocols. Fifth, it provides potential or current research subjects with information on which to base an informed consent decision, in an environment where there might be little information available other than that provided by the investigator or sponsor. Finally, it bolsters the impact of RAC review and public discussion by holding investigators and review agencies accountable for their actions, particularly if they are not in accord with the consensus view and recommendations of RAC.